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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/445,604	12/07/99	ABATANGELO G	515-4181

HM22/0329

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EXAMINER	
NGUYEN, Q	
ART UNIT	**PAPER NUMBER**
1632	10

DATE MAILED: 03/29/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No.	Applicant(s)	
	09/445,604	ABATANGELO ET AL.	
	Examiner	Art Unit	
	Quang Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondenc addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Applicants' amendments filed on 26 October 2000 and 17 January 2001 in paper No. 8 and No. 9, respectively, are acknowledged.

Claims 58-86 are pending in the present application.

It should be noted that the present application has been transferred to a new Examiner.

Response to Amendment

With regard to the Supplemental Amendment filed on 17 January 2001, it is noted that the paragraph requested to be inserted at page 8, lines 16-18 is in the middle of another existing paragraph. Clarification on proper page and line numbers for the inserted paragraph is requested.

Upon careful reconsideration of the application, following is the new ground of rejection.

Claim Rejections - 35 USC § 112

Claims 58-66 and 69-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* biological materials having limitations recited in claims 58 and 59, does not reasonably provide enablement for the same biological materials *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 58 and its dependent claims are drawn to a biological material comprising two components: a) at least one cell type selected from the group consisting of endothelial cells, glandular cells, skin adnexa and germinative cells of hair bulbs; and b) a biocompatible and biodegradable three-dimensional matrix comprising at least one hyaluronic acid derivative selected from the group recited in claim 58. Claim 59 and its dependent claims are directed to same biological material, wherein the cell type in component a) is cultivated in presence of a medium treated with fibroblasts or in a co-culture with fibroblasts. The claimed invention also includes the use of these biological materials such as use in human and veterinary surgery, in skin transplants, in skin and scalp transplants, in liver tissue transplants, in cases of insufficient insulin production, in surgery, in screening of medicaments or toxic substances, as a support and use for gene transfection.

The specification teaches by exemplification the isolation and cultured conditions in the presence of a three dimensional structure such as a non-woven HYAFF comprising a hyaluronic acid derivative for various cell types, including HUVEC, liver cell, islets of Langerhans and skin adnexa. The specification discloses that fragile cells such as endothelial cells, glandular cells and skin adnexa, germinative cells of hair bulbs and others can efficiently grow on a hyaluronic acid derivation matrix. Furthermore, the specification discloses optimal culture conditions for the growth of these cells in the hyaluronic acid derivative matrix, such as in the presence of a medium treated with fibroblasts or in a co-culture with fibroblasts seeded on the matrix at different time periods. The above evidence has been noted and considered. However,

the evidence can not be extrapolated to the instant broadly claimed invention for reasons discussed below.

As written, the claimed biological material encompasses both *in vivo* and *in vitro* materials having recited characteristics. As enablement required the specification to teach how to **make and use** the claimed invention, the instant specification fails to provide sufficient guidance or direction regarding to any *in vivo* use for the claimed biological materials. It is unclear whether the biological materials of the present invention could be maintained *in vivo* for a sufficient length of time in a host to carry out various *in vivo* functions contemplated by Applicants, such as for uses in human and veterinary surgery, in skin and scalp transplants, in liver tissue transplants, and in cases of insufficient insulin production. If the biological materials can not be retained for a sufficient period of time *in vivo*, then it is unclear what is the use for such materials. The claimed biological materials encompass autologous, allogeneic and xenogeneic cells. However, it is well known in the art that vigorous adverse host immune reactions would be elicited to reject the transplantation of xenogenic and allogeneic cells. Kohn (Clin. Exp. Immunol. 107:54-57, 1997) noted that even in allogeneic bone marrow transplantation for HLA-identical siblings, there is a 25 to 35% chance of mild to moderate graft versus host disease from donor-derived T lymphocytes responding to recipient antigens. This risk of graft versus host disease is significantly increased with the use of HLA-matched non-family members and non-HLA matched family members (See page 54, last paragraph of column 1 continues to column 2). The specification fails to provide sufficient guidance regarding how the biological materials of the instant

invention can overcome the adverse host immune reactions, such that they could be maintained *in vivo* for a sufficient period of time to accomplish their uses. In the absence of such teachings, it would have required undue experimentation without a predictable expectation of success for one skilled in the art to use the broadly claimed invention. The physiological art is also recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

With regard to claims 80 and 81 drawn to the biological material of the instant invention for use as a support for gene transfection and for use in gene transfection, genetically modified cells in such a biological material would further elicit reactive host immune responses. Even for transplanted autologous genetically modified cells, adverse host immune responses still present a challenge for the engraftment of these cells. This is because genetically modified cells express gene products associated with the vectors, selective antibiotic genes and the desired recombinant gene products which would be recognized by the host immune system as foreign proteins and adverse immune reactions would be mounted against the transplanted genetically modified cells. For example, adenoviral proteins for the situation wherein a recombinant adenovirus is utilized for transfecting the cells for treatment. Riddell et al. (Nature Med. 2:216-223, 1996) reported that five out of six patients seropositive for human immunodeficiency

virus developed cytotoxic T-lymphocytes responses specific to a novel protein and eliminated infused autologous CD8+ HIV-specific cytotoxic T cells transduced with a suicide gene encoding hygromycin phosphotransferase (See abstract). With the lack of guidance provided by the instant specification, it would have required undue experimentation without an expectation of success for one skilled in the art to make and use the claimed biological materials for use in *in vivo* gene transfection or as an *in vivo* support for gene transfection.

With regard to claims directed to the biological materials of this invention for other *in vivo* uses, as noted in the previous Office Action in paper No. 4 (pages 4-5), the instant specification fails to provide an enabling disclosure for the claimed biological materials comprising liver cells for liver tissue transplants, comprising islets of Langerhans cells for use in cases of insufficient insulin production, or comprising germinative cells of hair bulbs for use in scalp transplants. There is a complete lack of nexus between the *in vitro* tissue cultures disclosed by the present invention and the contemplated therapeutic effects expected to be achieved from *in vivo* uses for the same biological materials. It would have required undue experimentation without a predictable expectation of success for one skilled in the art to use the broadly claimed invention.

Accordingly, due to the lack of direction or guidance provided by the specification, the unpredictable nature physiological arts, and the breadth of the claims, it would have required undue experimentation without a predictable degree of success for one skilled in the art to **use** the broadly claimed invention.

To the extent of Applicants' responses (pages 7 and 8) that are applied to the rejection under 35 U.S.C. 112, First paragraph, they have been fully considered. Applicants discussed recent data showing that when the HYAFF scaffolds comprising either skin adnexa or islets of Langerhans or hepatocytes in co-cultures with human fibroblasts were implanted subcutaneously into **nude mice**, they retained their morphology after three weeks of implantation and became vascularized with new vessels originating from the surrounding vessels. After three weeks, HYAFF scaffolds underwent degradation and resorption, and the implanted reconstructed tissues comprise skin adnexa, Langerhans islets and hepatocytes. Applicants argued that since the claims are not directed to a therapeutic method but to the novel biological material, the enablement rejection should be withdrawn. Examiner respectfully find Applicant's argument and the recent data to be unpersuasive with respect to the new ground of rejection stated above for the following reasons.

With regard to the newly presented data, it is noted that **nude mice** lack a functional immune system, therefore it is still unclear whether the biological materials of the instant invention can be maintained *in vivo* for a similar period of time in a fully immunocompetent host. Although the claims do not recite therapeutic treatment or therapeutic results, treatment is the sole purpose for claims with specific recited uses. For examples, what other purposes would one use the biological material comprising islets of Langerhans for use in cases of insufficient insulin production or the biological material comprising liver cells for use in liver tissue transplants? It is noted that

enablement requires the specification teach how to make and **use** the claimed invention.

Therefore, claims 58-66 and 69-86 are rejected for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 58-86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 58, 59 and their dependent claims, the term "cell type" is unclear and renders the claim indefinite. The claimed biological material contains cells not cell type. Additionally, there is an improper Markush language in part a) of the claims, "consisting of endothelial cells, glandular cells, skin adnexa, germinative cells of hair bulbs", the term - - and - - should be inserted between skin adnexa and germinative cells of hair bulbs. The phrases "part or all of the carboxy functions" and "partial or total hyaluronic acid esters" are unclear. Clarification is requested because the metes and bounds of the claims can not be clearly determined. Furthermore, what is the relationship between the components a) and b) of the biological material? How do they exist to form the biological material? Clarification is requested.

In claims 61, 63, 83 and 85, the term "taken from" is unclear. The cells are usually isolated from the tissues rather than taken directly from the tissues as recited. Clarification is needed.

In claim 65, there is an improper Markush language which renders the claim indefinite, "and combinations...." should be replaced by - - or combinations... - -.

In claim 67, the phrase "contemporaneous presence of keratinocytes" is unclear. What do Applicants really mean? Clarification is requested.

Claim 68 is indefinite because it is dependent on a cancelled claim 29. The scope of the claim can not be determined.

In claim 85, there is an improper Markush language which renders the claim indefinite, "..sweat glands, hair bulbs and germinative cells.." should be - - sweat glands, hair bulbs or germinative cells.. - -.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 58, 61, 62, 64, 65, 69-72 and 74-81 are rejected under 35 U.S.C. 102(b) as being anticipated by Bellini et al. (WO 96/37519 with a published date of 28 November 1996; IDS).

The claims are to a biological material comprising: a) at least one cell type selected from the group consisting of endothelial cells, glandular cells, skin adnexa and germinative cells of hair bulbs; and b) a biocompatible and biodegradable three-

dimensional matrix comprising at least one hyaluronic acid derivative selected from the group recited in claim 58.

It should be noted that for composition claims, in this instance **an *in vitro* biological material**, intended use is not given any patentable weight in view of the prior art.

Bellini et al. teach a polysaccharide hydrogel material consisting of a crosslinked product of a functionalized derivative of alginic acid or hyaluronic acid, whose carboxylic groups are partially esterified (preferably 75% of the carboxylic groups) with an unsaturated aliphatic or an araliphatic alcohol, and the remaining carboxylic groups are partially salified with a cation selected from the group consisting of alkaline, alkaline earth metal cation or with tetraalkylammonium (page 2, first paragraph and page 4, lines 21-26). Additionally Bellini et al. teach that the hydrogel material can be prepared in the form of fibers, films, membranes, threads, gauzes and sponges, which are three dimensional objects or matrix (page 2, lines 16 and page 6, lines 1-10). Moreover, Bellini et al. teach that the hydrogel material can be used as supports of human cells such as keratinocytes, fibroblasts, osteocytes, chondrocytes, urocytes, stem cells, endothelial cells, Kupfer's and Langerhan's cells (page 6, lines 11-14). With respect to claims 61, it is well known that endothelial cells are isolated from tissues having blood vessels.

The hydrogel support taught by Bellini et al. meets all limitations recited in the claims, and thus Bellini et al. clearly anticipate the instantly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 58, 65, 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bellini et al. (WO 96/37519) in view of Cialdi et al.(U.S. Patent 6,027,741; Cited previously).

The claims are to a biological material comprising: a) at least one cell type selected from the group consisting of endothelial cells, glandular cells, skin adnexa and germinative cells of hair bulbs; and b) a biocompatible and biodegradable three-dimensional matrix comprising at least one hyaluronic acid derivative selected from the group recited in claim 58; the same wherein component b) is in the form of a nonwoven fabric.

It should be noted that for composition claims, in this instance **an *in vitro* biological material**, intended use is not given any patentable weight in view of the prior art.

Bellini et al. teach a polysaccharide hydrogel material consisting of a crosslinked product of a functionalized derivative of alginic acid or hyaluronic acid, whose carboxylic groups are partially esterified (preferably 75% of the carboxylic groups) with an unsaturated aliphatic or an araliphatic alcohol, and the remaining carboxylic groups are

partially salified with a cation selected from the group consisting of alkaline, alkaline earth metal cation or with tetraalkylammonium (page 2, first paragraph and page 4, lines 21-26). Additionally Bellini et al. teach that the hydrogel material can be prepared in the form of fibers, films, membranes, threads, gauzes and sponges, which are three dimensional objects or matrix (page 2, lines 16 and page 6, lines 1-10). Moreover, Bellini et al. teach that the hydrogel material can be used as supports of human cells such as keratinocytes, fibroblasts, osteocytes, chondrocytes, urocytes, stem cells, endothelial cells, Kupfer's and Langerhan's cells (page 6, lines 11-14). Bellini et al. do not teach that the hydrogel material can be prepared in the form of a nonwoven fabric or the use of sulfated hyaluronic acid to support the aforementioned human cells.

Cialdi et al. disclose that sulfated hyaluronic acid, hyaluronate esters and salts thereof can be used to prepare biomaterials in various forms such as gauzes, threads, gels, hydrogels, sponges, membranes, non-woven tissues and microspheres, all of which are three dimensional objects or matrix (See abstract and column 14, lines 53-60). Furthermore, Cialdi et al. teach that human umbiblical vein endothelial cells proliferate and exhibit better growth in culture medium containing sulfated hyaluronic acid than cells cultured in the medium containing hyaluronic acid or control medium (See example 16, columns 14 and 15).

Accordingly, at the time of the instant invention it would have been obvious to an ordinary skilled artisan to use sulfated hyaluronic acid in any of the form of gauzes, threads, gels, hydrogels, sponges, non-woven tissues, microspheres as supports for endothelial cells, Kupfer's and Langerhan's cells because Bellini et al. already teach

that polysaccharide hydrogel materials composing of crosslinked products of functionalized derivatives of hyaluronic acids can be used as supports for such cells. One of ordinary skilled in the art would have been motivated to use supports made up of sulfated hyaluronic acid disclosed by Cialdi et al., because Cialdi et al. already demonstrate in tissue culture that at least for endothelial cells, sulfated hyaluronic acid promotes the proliferation of endothelial cells. Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 67 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bellini et al. (WO 96/37519).

The claim is directed to a process for the preparation of a biological material according to claim 58, comprising the recited steps.

Bellini et al. teach a polysaccharide hydrogel material consisting of a crosslinked product of a functionalized derivative of alginic acid or hyaluronic acid, whose carboxylic groups are partially esterified (preferably 75% of the carboxylic groups) with an unsaturated aliphatic or an araliphatic alcohol, and the remaining carboxylic groups are partially salified with a cation selected from the group consisting of alkaline, alkaline earth metal cation or with tetraalkylammonium (page 2, first paragraph and page 4, lines 21-26). Additionally Bellini et al. teach that the hydrogel material can be prepared in the form of fibers, films, membranes, threads, gauzes and sponges, which are three dimensional objects or matrix (page 2, lines 16 and page 6, lines 1-10). Moreover, Bellini et al. also teach that the hydrogel material can be used as supports of human

cells such as keratinocytes, fibroblasts, osteocytes, chondrocytes, urocytes, stem cells, endothelial cells, Kupfer's and Langerhan's cells (page 6, lines 11-14). Bellini et al. do not teach explicitly the process of making the hydrogel material supports containing the aforementioned cells. However, at the effective filing date of the present application, the isolation of these cells and the seeding of these cells in the polysaccharide hydrogel materials of Bellini et al. as evident by the references supplied in the IDS. Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 58-61, 64-72, 76-83 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soranzo et al. (WO 96/33750) in view of Cialdi et al. (U.S. Patent 6,027,741), Bellini et al. (WO 96/37519) and Dorigatti et al. (U.S. Patent 5,520,916).

Applicants' inventions are drawn to biological materials according to claims 58 and 59, wherein the component a) comprises endothelial cells; and processes for the preparation of the same.

It should be noted that for composition claims, in this instance **an *in vitro* biological material**, intended use is not given any patentable weight in view of the prior art.

Soranzo et al. disclose an artificial human skin and method of making the same, comprising a microperforated membrane based on a hyaluronic benzyl ester with 75-100% esterification, such as Hyaff 11, in which keratinocytes are seeded on top of an underlying non-woven tissue of the same hyaluronic ester wherein fibroblasts are

seeded and may be co-cultured with the keratinocytes (Pages 13-14, claims 1-5 and 14-16). Among many potential uses for the artificial human skin, one of which is for use as a diagnostic device to test *in vitro* for medicants (claim 9). Soranzo et al. do not teach the use of endothelial cells, the use of sulfated hyaluronic acid, or the method of esterifying such in their artificial skin.

Dorigatti et al. disclose that the non-woven tissue of esterified hyaluronic acids, such as Hyaff 11, is comprised of esters of hyaluronic acid with aliphatic, araliphatic, cycloaliphatic or heterocyclic alcohols. They further disclose by exemplifications utilizing "partial esters" of 50%-100% esterification of carboxylic groups (Column 4, lines 24-31 and Examples 1-26).

Cialdi et al. disclose the use of sulfated hyaluronic acid and esters, wherein 25-100% of the carboxylic groups are in the form of esters. Cialdi et al. also disclose that sulfated hyaluronic acid, hyaluronate esters and salts thereof can be used to prepare biomaterials in various forms such as gauzes, threads, gels, hydrogels, sponges, membranes, non-woven tissues and microspheres, all of which are three dimensional objects or matrix (See abstract and column 14, lines 53-60). Furthermore, Cialdi et al. teach that human umbilical vein endothelial cells, isolated via collagenase digestion, proliferate and exhibit better growth in culture medium containing sulfated hyaluronic acid than cells cultured in the medium containing hyaluronic acid or control medium (See example 16, columns 14 and 15). Cialdi et al. also disclose that the sulfated hyaluronic acid functions like heparin to induce angiogenesis and neo-vascularization *in vitro* as demonstrated via a cell migration assay (Example 15).

Bellini et al. teach that the hydrogel material, made up of a crosslinked product of a functionalized derivative of alginic acid or hyaluronic acid, can be used as supports of human cells such as keratinocytes, fibroblasts, osteocytes, chondrocytes, urocytes, stem cells, endothelial cells, Kupfer's and Langerhan's cells (page 6, lines 11-14).

Accordingly, it would have been obvious to one of ordinary skilled artisan to generate biological materials of the instant claimed invention by co-seeding the endothelial cells, such as human umbilical veins, with the fibroblasts in the underlying non-woven tissue (three dimensional matrix) of the artificial human skin taught by Soranzo et al. This is because for the purpose of skin transplantation, one of ordinary skilled in the art would have been motivated to seed the endothelial cells to the underlying tissue rather than the upper layer of keratinocytes because the seeded endothelial cells would facilitate the process of angiogenesis such that the skin engraftment could receive nutrients from the host's vascular system. One would also be motivated to make a human umbilical vein endothelial cell/sulfonated hyaluronic ester matrix complex to promote vascularization as demonstrated by Cialdi et al. Besides, human umbilical vein endothelial cells can proliferate well in the presence of sulfonated hyaluronic acid, and that materials based on hyaluronic acid derivatives are taught by Bellini et al. to provide supports for endothelial cells, Kupfer's and Langerhan's cells, fibroblasts among many others. Note that there is no obvious reasons for one of ordinary skilled in the art to seed Kupfer's and Langerhan's cells in an artificial human skin. The isolation of endothelial cells, amplification on collagen-treated dishes and then transfer of the expanding endothelial cells into the underlying

non-woven artificial skin tissue of Soranzo et al. would have been within the scope of skills of an ordinary artisan. Again, one of ordinary skilled in the art would have been motivated to carry out the above modifications to generate a human artificial skin graft for transplantation or for screening medicants or toxic substances *in vitro* as disclosed by Soranzo et al. Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Applicant's arguments with respect to new claims 58-61, 64-72, 76-83 and 86 have been considered (Amendment in paper No. 8, pages 9-13) but are moot in view of the new ground(s) of rejection. In addition, Applicants should be noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusions

Claims 63, 73, 84 and 85 are free of the prior art. At the time of the instant invention, the prior art did not teach or fairly suggest the biological material having limitations recited in the claims.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Karen Hauda, at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Quang Nguyen, Ph.D.

PRIMARY PATENT EXAMINER
AU 1633
DAVE NGUYEN